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## **Inherited renal tubular dysgenesis: the first patients surviving the neonatal period**

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# Inherited renal tubular dysgenesis: the first patients surviving the neonatal period

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**Abstract** Renal tubular dysgenesis (RTD) is a clinical disorder either acquired during fetal development or inherited as an autosomal recessive condition. Inherited RTD is caused by mutations in the genes encoding the components of the renin-angiotensin system angiotensinogen, renin, angiotensin-converting enzyme and angiotensin II receptor type 1. Inherited RTD is characterized by early onset oligohydramnios, skull ossification defects, preterm birth and neonatal pulmonary and renal failure. The histological hallmark is the absence or poor development of proximal tubules. So far, all patients died either in utero or shortly after birth. We report the first patients with inherited

RTD surviving the neonatal period and still being alive. Genetic and functional analysis of the renin-angiotensin system contributes to the diagnosis of RTD. In conclusion, the clinical diagnosis of inherited RTD is easily missed after birth without renal biopsy or information on affected family members. Genetic and functional analysis of the renin-angiotensin system contributes to correct diagnosis.

**Keywords** Renin-angiotensin system · Renal tubular dysgenesis · Inherited

## Introduction

Renal tubular dysgenesis (RTD) is a clinical disorder either acquired during fetal development or inherited as an autosomal recessive condition. Acquired RTD is associated with drug-induced fetopathy, e.g., ACE-inhibitor, angiotensin II receptor antagonist, nonsteroidal antiinflammatory drug [8, 10, 11], twin-to-twin transfusion syndrome, major cardiac malformations [3] and severe liver disease [5]. A recent series on autosomal recessive RTD showed a uniformly severe course characterised by early onset oligohydramnios, persistent fetal anuria, pulmonary hypoplasia, severe refractory arterial hypotension and perinatal death [7]. Other features were also described, such as skull hypoplasia of the membranous bones resulting in wide cranial sutures and large fontanels. Histopathological hallmark of RTD is the absence or poor development of proximal renal tubules [7].

It has been suggested that the abnormality of the proximal tubules was secondary to primary defects in genes encoding factors involved in tubular growth and differentiation [13]. However, Gribouval et al. described homozygous and compound heterozygous mutations in the genes of

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the renin-angiotensin system encoding renin, angiotensinogen, angiotensin-converting enzyme or angiotensinogen II receptor type 1 in 11 individuals with RTD from 9 families [4]. This observation highlighted the crucial role of the renin-angiotensin system in human kidney development. It was suggested that renal lesions and early anuria resulted from chronic low perfusion pressure of the fetal kidney, a consequence of the renin-angiotensin system inactivity [7].

We report the first two patients with autosomal recessive RTD who survived the neonatal period and are still alive. In addition, functional analysis of the renin-angiotensin system is provided.

## Case reports

### Family A. Index patient 1

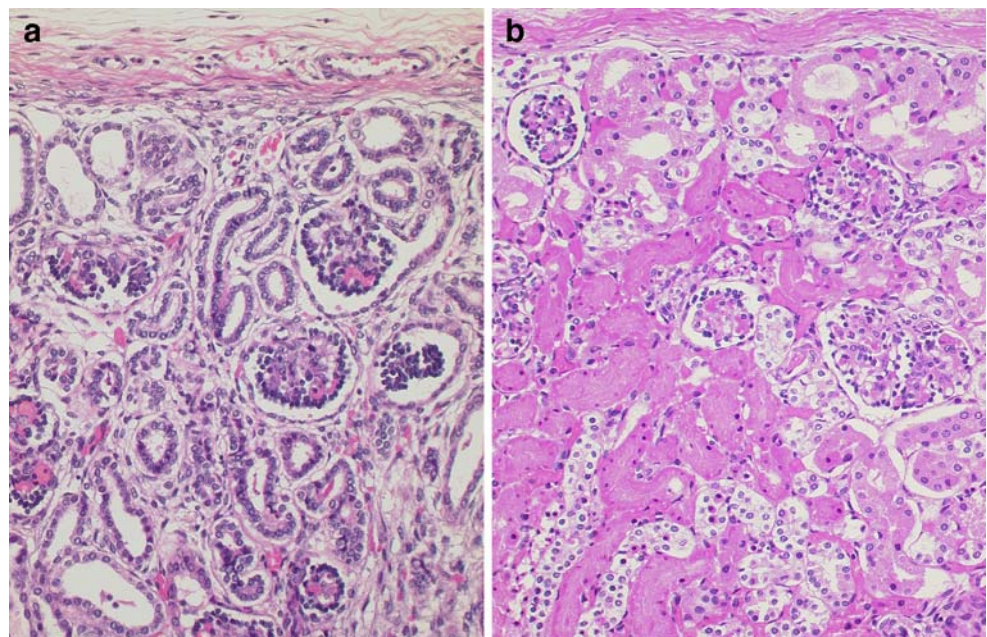
**Perinatal and neonatal outcome** This girl was the first child of consanguineous parents who are first cousins. During pregnancy the mother was not given any medication, in particular neither ACE-inhibitors, angiotensin II receptor antagonists, nonsteroidal antiinflammatory drugs nor COX-2-inhibitors. Oligohydramnios was detected at 32 weeks gestation. The girl was born in 1991 at 38 weeks and by caesarean section with normal body composition: weight 2,850 g (3rd percentile), length 51.5 cm (p50–90) and head circumference 31.8 cm (p10–50). Further clinical examination revealed a large anterior fontanelle, a wide gap of the sagittal sutures and bilateral pes calcaneus and ulnar deviation of both hands. Postnatal adaptation was compli-

cated by meconium-stained amniotic fluid and respiratory distress syndrome as a consequence of pulmonary hypoplasia and bilateral pneumothorax, requiring ventilation for 4 weeks. Since birth, the girl had been hypotensive and anuric, refractory to therapy with large fluid supplements, catecholamines and diuretics (furosemide). Thus, peritoneal dialysis was started on day 2. On day 3, diuresis started, and dialysis could be ceased on day 4. Arterial hypotension persisted and the girl required continuous long-term administration of both adrenaline (11 days) and dopamine (20 days). The peak plasma creatinine concentration (369  $\mu\text{mol/l}$ ) was reached on day 9. Renal ultrasound showed normal size, but reduced corticomedullary differentiation. Renal biopsy at the age of 4 days showed immature glomeruli, undifferentiated tubules and only a few normal proximal tubules, and did not allow specific classification (Fig. 1a). Biopsies of liver, skin, muscle and placenta showed normal tissue.

The girl was discharged at the age of 2 months with impaired renal function (plasma creatinine 139  $\mu\text{mol/l}$ , normal <40). The presumptive diagnosis was renal ischemic injury and acute tubular necrosis due to asphyxia.

**Long-term outcome** The renal function remained impaired. Plasma creatinine concentration reached its nadir (62  $\mu\text{mol/l}$ ) at 2 years of age with a steady increase thereafter: 92  $\mu\text{mol/l}$  at 5 years, 89  $\mu\text{mol/l}$  at 8 years with a glomerular filtration rate of 35 ml/min per 1.73 m<sup>2</sup> (Cr-EDTA clearance) and 99  $\mu\text{mol/l}$  at 10 years. Casual blood pressure was always in the lower range of normal. Growth, psychomotor and neurological development, and puberty (menarche at 13 years) were normal.

**Fig. 1** **a** Renal biopsy of index patient 1 (family A) at the age of 4 days: Immature glomeruli, undifferentiated tubules (HE, 12 $\times$ ). **b** Normal renal tissue of a newborn (HE, 12 $\times$ )



Currently, at the age of 15 years, she is in good general condition. Anthropometry is normal: height 156 cm (p10–25), weight 62 kg (p75–90) and head circumference 55 cm (p75–90). There is moderate chronic renal failure with an elevated plasma creatinine (188  $\mu\text{mol/l}$ ) and an estimated glomerular filtration rate of 48 ml/min per 1.73 m<sup>2</sup> (Schwartz-formula) and moderate proteinuria (<1.0 g/day). Medication includes calcitriol and erythropoetin, but no antihypertensive drugs. Casual systolic blood pressure is 93 mmHg (<p50; p50=106 mmHg) and diastolic blood pressure is 66 mmHg (p50–75; p50=64 mmHg). Ambulatory 24-h mean, systolic and diastolic arterial pressure is 79 mmHg (p50), 102 mmHg and 67 mmHg, respectively. Ultrasound shows normal sized kidneys (left: 9.9 cm; right: 8.5 cm) with hyperechogenic parenchyma and loss of corticomedullary differentiation.

#### Family A. Healthy brother

He was the second child, born at term (40 2/7 weeks) after an uncomplicated pregnancy with a birth weight of 4,460 g (> p90). Postnatal adaptation and further development were uneventful. Currently, at the age of 11 years, he is healthy. Renal function is normal (plasma creatinine 62  $\mu\text{mol/l}$ ), and there is no proteinuria. Casual blood pressure-systolic blood pressure 99 mmHg (<p50; p50=105 mmHg), diastolic blood pressure 58 mmHg (<p50; p50=62 mmHg) and 24-h ambulatory blood pressure (mean 69 mmHg=p3) are in the lower normal range. Renal ultrasound shows two normal kidneys.

#### Family A. Patient 2

When the index patient was 8 years old (1999), the mother became again pregnant. She was not given any medication during her third pregnancy. Severe oligohydramnios was detected at 25 weeks gestation. Two normal-sized kidneys were visible, but the bladder was always empty. Karyotyping was normal (46, XX). The offspring was born preterm at 36 weeks gestation by urgent caesarean section because of premature rupture of the fetal membranes and meconium-stained amniotic fluid with a weight of 2,250 g (p10–50), length of 43 cm (<p10) and head circumference of 31 cm (p10–50). Postnatal clinical examination showed features of anhydramnios with severe joint contractures of hands and feet. She immediately developed severe respiratory distress syndrome with bilateral pneumothorax requiring ventilation. In addition, severe hypotension (maximal mean arterial blood pressure  $\leq 40$  mmHg) persisted despite large fluid supplements and catecholamines. Renal ultrasound confirmed normal-sized, but hyperechogenic kidneys with lost corticomedullary differentiation. The girl remained

anuric and plasma creatinine rose to 260  $\mu\text{mol/l}$ . The clinical condition deteriorated, and the child died at the age of 4 days. The autopsy revealed renal tubular dysgenesis and hyaline membrane disease, but no lung hypoplasia.

Subsequently, the diagnosis of the index patient was reevaluated and familial, autosomal recessive RTD was suggested.

#### Family A. Patient 3

When the index patient was 13 years old (2004), a second sister was born suffering the same course as patient 2. Again, the mother had not taken any medication during pregnancy. The girl was born preterm at 35 weeks gestation in a peripheral hospital after a pregnancy with oligohydramnios (detected at 20 weeks gestation) with a birth weight of 2,210 g (p10–50), length of 44 cm (p10–50) and head circumference of 30.4 cm (p10–50). Postnatal clinical examination showed features of oligohydramnios with joint contractures of the feet, knees and hip. She immediately developed severe respiratory distress syndrome with bilateral pneumothorax requiring ventilation and referral to a tertiary-care center. In addition, severe hypotension persisted despite large volumes and catecholamines. Renal ultrasound confirmed normal-sized, but hyperechogenic kidneys with lost corticomedullary differentiation. The girl remained anuric and died at day 2. The parents did not consent to autopsy and genetic analysis.

#### Family A. Healthy parents

Both parents-mother at 34 years and father at 38 years-are healthy. Casual blood pressure is normal (mother 113/70 mmHg; father 116/65 mmHg).

#### Family A. Genetic analysis

The genetic analysis of the renin-angiotensin system became available in 2005 [4], revealing in the index patient 1 a homozygous mutation in the AGT gene encoding angiotensinogen (R375Q; 1124 G  $\rightarrow$  A). The G to A transition at position 1,124 results in a missense change affecting a highly conserved arginine in the serpin domain of the protein. As this mutation involves the final nucleotide of exon 3, it is predicted to severely affect splicing and result in a truncated serpin domain. Angiotensinogen, a plasma serpin protease inhibitor, is cleaved by renin to generate angiotensin I from its N-terminal region. The serpin framework is necessary for correct cleavage of the peptide; hence, this truncating mutation is expected to lead to a defect in the generation of angiotensin I [4]. Patient 2 was also homozygous, whereas the brother and the parents were heterozygous carriers. Patient 3 was not



**Table 1** Functional analysis of the renin-angiotensin system in family A

	Angiotensinogen (ng/ml)	Renin (pg/ml) total-active		Plasma renin activity (ng/ml/h)
Patient 1	21.4	795	199	0
Heterozygous brother	247.2	403	160	1.7
Normal controls*	1,024±275	288±75	22±11	1.5–3.0

\*Normal values (mean ± SD) (9)

analysed. Written informed consent was obtained from the patient and the parents.

#### Family A. Functional analysis of the renin-angiotensin-system

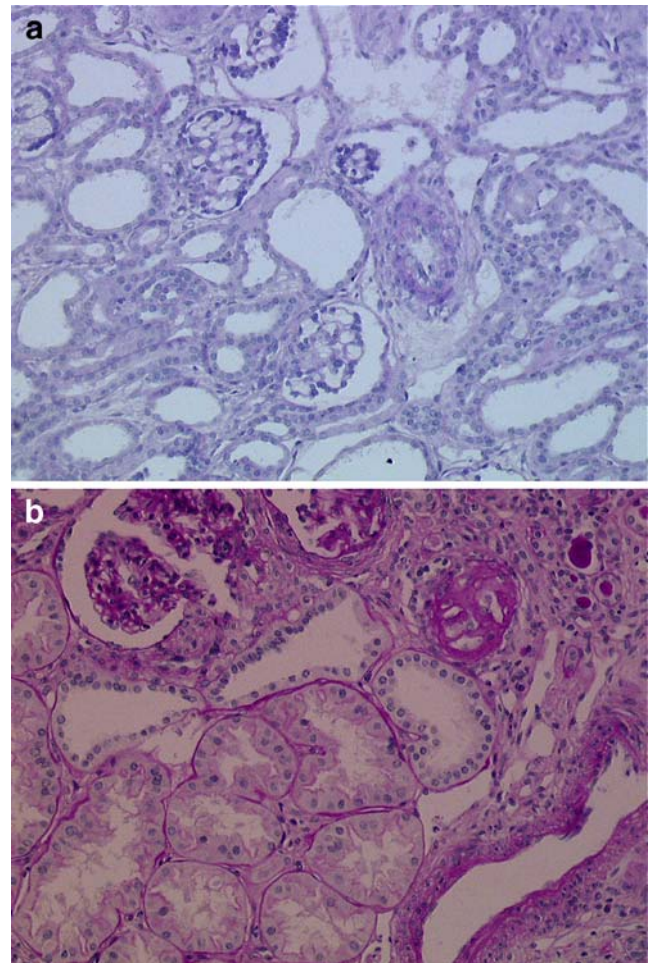
Angiotensinogen, plasma total and active renin, and plasma renin activity were measured in the index patient and her healthy brother (Table 1). Angiotensinogen was measured by generation of angiotensin I (AI) after full hydrolysis by an excess of recombinant renin at pH 5.7 as previously described [9] and expressed as ng AI/ml. Total plasma renin (= prorenin + active renin) concentration was determined with the Cisbio kit after trypsin activation as previously described [9]. The plasma renin activity is defined as renin-dependent conversion of angiotensinogen to angiotensin I, measured as generation of angiotensin I in ng/ml/h; angiotensin I was measured by RIA at pH 5.7. The homozygous index patient 1 showed extremely low angiotensinogen concentration; subsequently, conversion to angiotensin I, i.e., plasma renin activity, was low despite very high renin concentration. The heterozygous brother showed reduced plasma angiotensinogen concentration; plasma renin activity was at the lower limit of normal despite elevated renin concentration.

#### Family B. Index patient 1

**Perinatal and neonatal outcome** This girl was the second child of consanguineous parents who are first cousins. The first born boy was healthy. The follow-up of pregnancy was insufficient, but the mother was not given any medication. Oligohydramnios was detected shortly before birth. The girl was born (1994) preterm at 35-week gestation with a birth weight of 2,520 g (p50–90), a length of 48 cm (p50–90) and a head circumference of 30 cm (p10–50). Clinical examination showed wide cranial sutures and hypotonia. Postnatal adaptation was complicated by mild respiratory distress syndrome requiring oxygen for 24 h, anuria and hypotension (44/19 mmHg). The girl was treated with albumin infusions, dopamine (5 days) and furosemide (7 days). Renal ultrasound showed two kidneys (50 and 53 mm), with hyperechogenicity and no corticomedullary differentiation. Karyotype was normal. On day 9, plasma creatinine concentration reached a peak (625 µmol/l).

Peritoneal dialysis was started and a renal biopsy was performed. Histology (Fig. 2a) showed immature glomeruli, rare tubular sections characterised by dilatation, increased interstitial tissue and thickening of arteriolar musculature suggesting renal tubular dysgenesis, and diffuse positivity for anti-epithelial membrane antigen (EMA).

Diuresis started at 2 months of age. A second biopsy was performed at 4 months of age, showing tubulointerstitial



**Fig. 2** **a** First renal biopsy of index patient 1 (family B) in the neonatal period (PAS ×120): Immature glomeruli, small number and irregular size of tubules, increased interstitial tissue and thickening of arteriolar musculature. **b** Nephrectomy specimen (PAS ×120): One hypertrophic nephron with large proximal and dilated distal tubules with adjacent area showing interstitial fibrosis with tubular atrophy and glomerular sclerosis

lesions with tubular microcysts. However, few proximal tubules with epithelial damage were present. A second look of the first biopsy suggested minimal proximal tubular differentiation.

**Long-term outcome** Peritoneal dialysis could be stopped at the age of 5 months. Chronic renal failure persisted with renal anemia and secondary hyperparathyroidism. Blood pressure remained normal, within lower values. Glomerular filtration rate (inulin clearance) was 15 and 9 ml/min per 1.73 m<sup>2</sup> at 16 months and 4 years, respectively. Growth was <p3, but improved on growth hormone treatment. At the age of 4 years, the girl underwent renal cadaveric transplantation and both native kidneys were further removed due to massive polyuria. Pathology examination showed large areas of interstitial fibrosis with atrophic tubules and sclerotic glomeruli intermingled with some foci of strikingly hypertrophic nephrons (Fig. 2b). In preserved hypertrophic nephrons, CD15 was normally expressed in proximal tubules and EMA in distal tubules. Severe arterial and arteriolar changes were still present.

The girl is currently 10 years old with a glomerular filtration rate of 47 ml/min per 1.73 m<sup>2</sup>. Psychomotor and cognitive development is normal.

**Genetic and functional analysis** Mutational analysis revealed a homozygous mutation in the REN gene encoding renin (S135Y). Plasma active renin measured by radioimmunoassay during the neonatal period was very low (<2.5 ng/l; normal range for neonates: 24 to 850 ng/l).

Written informed consent was obtained from the parents.

#### Family B. Patient 2

The third pregnancy was terminated at 30-week gestation because of severe oligohydramnios and renal ultrasound showing undifferentiated hyperechogenic kidneys. The child was stillborn. No further analysis was available.

#### Family B. Healthy brother

He was the first child (1988), born at term after an uncomplicated pregnancy. Postnatal adaptation and further development were uneventful. Currently, at the age of 19 years, he is healthy.

#### Family B. Healthy parents

Both parents (mother 42 years and father 46 years) are currently healthy and have normal blood pressure (130/70 and 120/80 mm Hg, respectively).

## Discussion

Renal tubular dysgenesis is a clinical disorder either acquired during fetal development [3, 5, 11] or inherited as an autosomal recessive disease [1, 4, 7]. Recently, it has been shown that autosomal recessive RTD is genetically heterogeneous and caused by mutations in the genes encoding components of the renin-angiotensin system, i.e., angiotensinogen, renin, angiotensin-converting enzyme and angiotensin II receptor type 1 [4]. The clinical course of inherited RTD has been uniformly severe: Pregnancy of affected fetuses was either terminated or the children died in utero or during the early postnatal period within 4 h to 36 days [7]. We report the first patients with inherited RTD surviving the neonatal period and still being alive.

The prenatal hallmark of inherited or acquired RTD is the combined finding of (1) oligo- or anhydramnios, detected between 16 and 33 week gestation, mostly around 20 week, and persisting throughout gestation leading to various degree of Potter sequence and (2) renal ultrasound showing normal-sized and -shaped kidneys with hyperechogenicity and poor corticomedullary differentiation of various degrees. The bladder is often empty.

Affected children of acquired or inherited RTD are mostly born preterm. The neonatal course is dominated by severe respiratory distress secondary to lung hypoplasia and pneumothorax, persistent and therapy refractory hypotension and anuria. Further clinical examination shows normal body composition, skull ossification defects and limb deformities as a consequence of oligohydramnios. The renal ultrasound examination after birth shows similarities to the prenatal findings with hyperechogenic, but normal-sized and -shaped kidneys. Histopathological hallmark is the absence or poor development of proximal tubules.

Family history, drugs administered during pregnancy (i.e., ACE inhibitors, angiotensin II receptor antagonists and nonsteroidal antiinflammatory drugs), clinical examination revealing further malformations [3, 5] and postnatal course may allow differentiation between acquired and inherited RTD. The majority of children with acquired drug-induced RTD survived the neonatal period [8, 10, 11].

The genetic analysis in family A and B revealed a homozygous mutation of the AGT gene and renin gene, respectively. Functional analysis in family A of the homozygous patient and her heterozygous brother showed a gene-dose effect with reduced angiotensinogen and plasma renin activity in both, but much more apparent in the homozygous patient. Both siblings' blood pressures (casual and 24-h ambulatory) was in the lower range of normal. The heterozygous brother, however, had a normal pre-/postnatal development and renal function.

The clinical diagnosis of inherited RTD can easily be missed unless a renal biopsy is performed or information on

affected family members is available. Patients might-as the index patient 1 in family A-be misdiagnosed with acute tubular necrosis and renal failure secondary to neonatal asphyxia. Thus, the incidence of inherited RTD is probably underestimated. So far, all reported children with inherited RTD died either in utero or shortly after birth. We report the first patients surviving the neonatal period and still being alive. Pregnancy and early neonatal course of the index patients were comparable to the deceased siblings in family A and the patients reported in the literature [1, 4, 6, 7]. One can only speculate which factors might have contributed to the long-term survival of the two reported patients. Polymorphism in other genes, affecting arterial tone and renal perfusion, may be involved in the discordant course among affected siblings as shown in both families. Differential diagnosis includes inherited renal anomalies caused by mutations or deletions in the hepatocyte nuclear factor-1beta [12] and PAX2 [2] genes. These genes, however, were not analysed in the reported patients.

The more favourable outcome in these two patients had some influence on genetic counselling in our units: If inherited RTD is suspected in a fetus, parents are informed that the majority of affected fetuses will die either in utero or shortly after birth, but that there is a (yet unpredictable) chance for survival. If the pregnant woman wants to give birth to her child, we strongly advise to deliver the child in a tertiary-care center.

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